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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,794	06/08/2001	Suzanne A. W. Fuqua	UTSK:348US/MBW	5270

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/877,794	Fuqua et al
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 4, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above, claim(s) *2 and 5* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3, and 4* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5'*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed August 4, 2003 (Paper No. 14) in response to the Office Action of June 20, 2003 (Paper No. 12) is acknowledged and has been entered. Claims 6-21 have been canceled. Claims 1-5 are pending in the application and Claim 1 as it is drawn to limitations other than those drawn to TIE-2 as well as claims 2 and 5 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 3 and 4, drawn to TIE-2 are currently under prosecution.

2. Applicant's election without traverse of Group I, claims 1, 3 and 4 drawn to TIE-2 in Paper No.12 is acknowledged. It is noted that Applicant understands that Claim 1 has been determined to be a linking claim with regard to the Groups 1-1171 and that the various restriction requirements amongst the Group 1-1171 inventions are subject to the non-allowance of linking claim 1. Although claim 1 is linked to 1171 inventions, the restriction requirement clearly separates the groups linked to claim 1, which is drawn to assay of seven different markers each of which are groups that are materially distinct methods as stated in Paper No. 12 on page 44. Thus claim 1 is drawn to seven distinct groups, each of which is linked to other claims by claim 1 as set forth in Sections 3-9, pages 3-20 of Paper No. 12. The groups linked by claim 1 drawn to TIE-2 are groups 1-194

Specification

3. The specification on page 1 should be amended to reflect the status of the provisional parent application. Further, it is improper to claim priority to a provisional application. The appropriate form is as follows:

"This application claims benefit to provisional application **********, filed **, now abandoned."

Appropriate correction is required.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because non-dated alterations to the address of Inventor Friedrichs have been made to the oath or declaration. See 37 CFR 1.52 (c).

Drawings

5. The brief description of the drawings is objected to because Figure 1 consists of Figures 1A, 1B and 1C but neither the drawing nor the brief description describes Figures 1A, 1B or 1C.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

7. Claims 1, 3 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of detecting tamoxifen-resistant

MCF-7 breast cancer cells comprising assaying for the overexpression of a high molecular weight, 220 kDA putative TIE-2 related polypeptide, does not reasonably provide enablement for a method of detecting tamoxifen-resistant breast cancer cells comprising assaying for TIE-2 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to are a method of detecting tamoxifen-resistant breast cancer cells. This includes any tamoxifen-resistant breast cancer cells from any species including a human by detecting any TIE-2 related polypeptide.

The specification teaches that the precise mechanisms underlying acquired tamoxifen resistance remain poorly understood.(p. 2, lines 29-30). Breast cancer is a heterogeneous disease and the development of tamoxifen resistance is probably multifactorial, thus complex changes in patterns of gene expression may accompany the resistant phenotype. The present invention satisfies a long-standing need by identifying changes in gene expression that are associated with the development of tamoxifen resistance (p. 3, lines 1-5). The present invention is the first to report an association between the development of tamoxifen resistance and the differential expression of angiogenic factors and angiogenic receptors (p. 3, lines 10-12).

Differential expression of the gene encoding TIE-2 is reported in the specification to be associated with tamoxifen-resistant breast cancer (p. 3, lines 30-31). One embodiment of the instant invention comprises a method for detecting the

expression of TIE-2 gene products in a biological sample for the diagnosis of tamoxifen-resistant breast cancer (p. 44, lines 11-15). The TIE-2 polypeptide detected in the specification is a high molecular weight, 220 kDA putative TIE-2 related protein, (see description of Figure 7) which differs from that expressed in normal cells which express a TIE-2 protein of approximately 140 kDA (see the Description of Figure 8, p. 7). Antibodies can be used to characterize TIE-2 in diseased/healthy tissues to provide a screen for the presence of malignancy through such techniques as ELISA and Western blotting (p. 53, lines 25-30). Materials and methods are disclosed wherein MCF-7-derived tumors are assayed to demonstrate expression (page 70) of TIE-2, wherein cells from estrogen-stimulated tumors prior to tamoxifen treatment as well as cells from tamoxifen resistant tumors were obtained (p. 70, lines 5-11). Pulverized frozen tumors were assayed by Western blot (p. 70). Using this model it was found that expression of TIE-2 mRNA and protein are upregulated in tamoxifen resistant MCF-7 cell line tumor as compared to tamoxifen-sensitive and estrogen stimulated MCF-7 cell line cancers. Although angiogenic factors and receptors were known as bad prognostic markers for breast cancer, this is an unexpected result, this is the first time that a correlation between expression levels for angiogenic factors and receptors and tamoxifen-resistant breast cancer has been reported (p. 76, lines 10-16). These results demonstrate that TIE-2 is a positive marker for tamoxifen-resistant breast cancer and assays for increased

expression of this marker may be used to differentiate between tamoxifen-resistant and tamoxifen-sensitive forms of breast cancer (p. 77, lines 8-15).

One cannot extrapolate the teaching of the specification to the scope of the claims because the invention is based on tumor cell line data that is not commensurate in scope with the *in vivo* condition. In particular, Dermer (Bio/Technology, 1994, 12:320) teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary -type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cultured cells exhibit characteristics different from those *in vivo*. Further, Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded. This is exemplified by the teachings of Zellner et al (Clin. Can. Res., 1998, 4:1797-17802) who specifically teach that products are overexpressed in glioblastoma (GBM)-derived cell lines which are not overexpressed *in vivo*, Drexler et al further teach that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the bona fide cancer cell lines it is difficult to prove

that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactual antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). In particular, as drawn to the 220 kDa putative TIE-2 related protein, it would appear that the high molecular weight TIE-2 related protein is a product of a change in chromosomal constitution because the specification reports that the apparently "normal" TIE-2 is a 140 kDA protein. It could not be predicted, nor could it be determined, based on the information in the specification, whether this apparent change in chromosomal constitution is an artifact of the cell line used to produce the data or whether this alteration would occur in any primary or metastatic breast tumor in, for example, a human patient or that this change would be in any way associated with tamoxifen-resistant breast cancer cells. Further, given the known artifactural nature of cell lines, it cannot be predicted nor can it be determined from the information in the specification whether

or not any TIE-2 polypeptide would be overexpressed in primary or metastatic tamoxifen resistant breast cancer tissue, for example in a human patient. This is especially true given the clear admission on the record that the present invention is the first to report an association between the development of tamoxifen resistance and the differential expression of TIE-2.

Further, even if the RNA gene product of the TIE-2 gene were to be overexpressed, it could neither be predicted nor would it be expected that a similar overexpression of protein would also be found because evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels in cancer tissues. For instance, Hell et al (Laboratory Investigation, 1995, Vol. 73, pp. 492-496) teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cancer cell will be paralleled at the protein level due to

complex homeostatic factors controlling translation and post-translational modification.

Finally, one cannot extrapolate the teaching of the specification to the scope of the claims because this single example, drawn to a cell culture tumor model has not established that the overexpression of TIE-2 is a "marker" for tamoxifen resistant breast cancer. In particular, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to the use of TIE-2 protein overexpression for identifying tamoxifen-resistant breast cancer. Tockman et al teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Pertinent to the instant rejection, there is no evidence presented in the specification or the art of record that the overexpression of TIE-2 protein is in any way associated with tamoxifen resistant breast cancer, for example, in humans wherein the use of this marker for determination of tamoxifen resistant breast cancer is clearly contemplated by the Inventors. Tockman goes on to teach that markers have clear biological plausibility and **if validated** (emphasis added) can be used for population screening (p. 2713s, col 1). The essential element of the validation of a marker is

the ability to test the marker on clinical material obtained from subjects monitored and to link those marker results with subsequent clinical confirmation of, in the instant case, tamoxifen-resistant breast cancer. This irrefutable link between marker and acknowledged, in this case, tamoxifen-resistance, is the essence of a valid marker (p. 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated (p. 2716s, col 2). Again, the specification teaches that this is the first time that a correlation between expression levels for angiogenic factors and receptors and tamoxifen-resistant breast cancer has been reported and clearly states that the results disclosed demonstrate that TIE-2 is a positive marker for tamoxifen-resistant breast cancer and assays for increased expression of this marker may be used to differentiate between tamoxifen-resistant and tamoxifen-sensitive forms of breast cancer. However, given the unexpected nature of the results, given that the specification clearly states that this is the first time that a correlation between expression levels for angiogenic factors and receptors and tamoxifen-resistant breast cancer has been reported, given the well known differences between cultured cell line derived tumor cells and primary tumor cells, given the known artifactural nature of cell lines, given that the detected polypeptide does not appear to be TIE-2, but rather a putative TIE-2 related protein observed in a cell-line derived tumor, given the art recognized necessity to validate cancer markers in order to determine if they in fact do what is suggested, it cannot be

predicted and one of ordinary skill in the art would not believe that it is more likely than not that the invention will function as claimed based only on the MCF-7 tumor model presented. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

It is noted that presentation of objective data demonstrating that upregulated expression of 220 kDA putative TIE-2 related protein in primary human breast tumors detects/diagnoses/provides a predication of the existence of tamoxifen-resistant breast cancer cells would obviate this rejection.

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
September 25, 2003